Remarks

Claims 1-13 were initially pending in the subject application. In response to a restriction requirement (dated January 13, 2003), claims 2 and newly presented claims14-18 were elected for examination on February 12, 2003. Claim 2 has been canceled in the amendment filed on this date and claims 15-21 have been amended. Claims 22–31 have been added. Support for these new claims and the amendments to the pending claims can be found throughout the subject specification, including, for example, the previously pending claims and paragraphs 22-24 and 714. Favorable consideration of the claims now presented, in view of the remarks and amendments set forth herein, is earnestly solicited.

Claims 14-18 have been rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility due to its not being supported by a specific, substantial, and credible utility or, in the alternative, a well-established utility. The Office Action argues that the claimed invention, the polypeptide sequence of SEQ ID NO: 42 is not supported by a specific utility because the disclosed uses of the polypeptide are not specific and are generally applicable to any cytogram polypeptide. It is respectfully submitted that the fact that the claimed invention can be used in a fashion similar to known cytogram polypeptides is indicative of the polypeptide having a "well-established" utility and that the claimed invention meets the requirement of 35 U.S.C. § 101.

The Office Action also argues that the subject invention is not supported by a substantial utility because the claimed sequence is not connected to a specific or readily available utility. The Office Action further states that Applicant should explicitly identify a specific, substantial, and credible utility for the claimed invention and that a probative relationship between any evidence of record and the originally disclosed properties of the claimed invention. Finally, the Office Action notes that the application has identified SEQ ID NO: ID NO: 42 as a cytogram, a splice variant of GMP-17. The Office Action continues that it is unclear whether the claimed invention has been tested for its asserted biological activity, that it is well-known in the art that sequence similarity does not reliably correlate with structural similarity, and that structural similarity does not reliably result in similar or identical biological activities. Applicants respectfully traverse.

Applicants note that the Office Action cites five articles illustrating the unpredictability of the relationship between sequence, structure and function to support the assertion that the claimed

polypeptide has no utility and that one skilled in the art would not know how to use the claimed polypeptides. Applicants' respectfully disagree with this assertion and note that none of the cited references are directed to polypeptides that are splice variants of known polypeptides. For example, Attwood discusses the use of bioinformatics for structure and function predication; however the reference is silent with respect to splice variants of polypeptides having known function and uses. Likewise, Lopez *et al.* discusses the annotation of the *Chlamydia trachomatis* genome and fails to address splice variants of human polypeptides that have known function.

Further, it is respectfully submitted that, based upon the teachings of Wells *et al.*, one of skill in the art would have believed that sequence comparison is a powerful and reliable tool to identify gene function. This reference teaches the identification of novel chemokines using EST databases and bioinformatics tools such as the TblastN program. In particular, several new CC chemokines were first identified using sequence comparison programs (see, *e.g.*, page 547, first column):

> There were far more CC chemokines, eight in total, which at the time of search were novel, although publications on several of them have appeared in recent months (...).

Additionally, Wells *et al.* clearly state (at page 546, first column and page 549, first column [emphasis added]) that sequence comparison is reliable for identifying the function of a protein:

> These features make the identification of novel chemokines in sequence databases relatively easy because *even though the overall sequence identity levels between chemokines may be as low as 20%*, the cysteine spacings and hydrophobicity may still be used to detect novel chemokine sequences.
>
> (...) [T]he most interesting of the novel chemokines discovered from the EST database was that based on the EST Z44443, *where there are three amino acids residues separating the first two cysteine residues.*

In view of these statements, one of skill in the art would have no reason to believe that the biochemical activity of a protein exhibiting less than 100% sequence similarity to a known protein would not be the same as, or similar to, that of the known protein. Indeed, the reference clearly

indicates that polypeptide exhibiting as little as 20% identity can share similar or identical biological activity.

Another reference cited, Gerhold *et al.*, presents a discussion of EST databases, but does not specifically discuss the relationship between sequence and function. This publication does not provide any data proving the unpredictability of the relationship between sequence and function. On the contrary, it highlights the importance of sequence comparison as a tool for identifying gene function (see, *e.g.*, page 980, second column):

> The ability to readily identify and analyze gene homologs from different organisms will accelerate the determination of protein function from gene sequence.

Russel *et al.*, another of the cited references, discusses the relationship between three-dimensional (3D) structure and sequence similarity and function and is not considered relevant to the issue at hand. Russel *et al.* discuss the unpredictability of 3D structures at page 346, second column:

> All of the results suggest that proteins can adopt very similar folds using almost completely different interactions, and that proteins having similar 3D structures can have little in common apart from a scaffold of common core secondary structures.

However, Applicants respectfully submit that the function of the claimed polypeptide is not based on its 3D structure, but on the fact that it is a splice variant of a known and characterized polypeptide. Russel *et al.* do not suggest that two proteins sharing little or no sequence similarity exhibit different functions. On the contrary, as stated at page 348, first column:

> [B]oth the sequence and the structure of similar proteins can evolve beyond recognition even when function is conserved.

Thus, it is respectfully submitted that the cited references fail to support the Patent Office's conclusion that the claimed invention lacks a patentable utility.

As also set forth in the Office Action of April 14, 2003, the subject invention has been rejected on the grounds that the polypeptide sequence of SEQ ID NO: 42 is not supported by a

specific utility because the disclosed uses of the composition are not specific and are generally applicable to any cytogram polypeptide. Applicants respectfully submit that the subject application discloses a number of specific uses for the claimed polypeptide and that such uses fulfill the utility requirements of 35 U.S.C. § 101.

For example, the specification sets forth (at paragraphs 710, 712, and 713) that one embodiment of the invention is directed to a composition comprising an antibody recognizing a cytogram polypeptide sequence of SEQ ID NO:42 or a cytogram polypeptide fragment. Another embodiment is directed to:

> ... methods of detecting or quantifying activated NKs and CTLs comprising the steps of: i) contacting a body fluid, a tissue sample or a mammalian cell culture with an antibody that specifically binds to cytogram polypeptides, and ii) detecting the antibody in the sample using any detectable signal. Compounds such as, e.g., alkaline phosphatase, peroxidase, FITC, rhodamine, Texas-Red, biotin and digoxigenin can be used to provide a detectable signal. The detection of the signal may be carried out using immunohistological or immunofluorescing processes that are well-known to those skilled in the art. The antibody that specifically binds to cytogram polypeptides may be directly labeled with the compound giving the detectable signal. Alternatively, the antibody that specifically binds to cytogram polypeptides is not labeled and detection of the signal occurs indirectly by using labeled secondary antibodies. In a preferred embodiment, detecting activated NKs and CTLs can be used to measure the effect of a test compound on CTL or NK activity in mammalian cell cultures. In another preferred embodiment, such methods can be used to monitor the effects of a treatment aiming to increase or decrease CTL or NK activity in a patient, or to detect the beginning of a graft rejection reaction in a patient.

It is submitted that such teachings provide a credible, specific and readily available utility for the claimed polypeptide. Namely, the polypeptide can be used to generate antibodies that are capable of specifically binding to known cytogram polypeptides (such as GMP-17) or the polypeptides of the subject invention and such antibodies can be used to detect activated T lymphocytes or natural killer (NK) cells involved in, for example, allograft rejection or graft versus host disease (GVHD).

As is apparent from the attached article by Meehan *et al.*, human renal allografts can be immunohistochemically stained using antibodies to GMP-17 (also known as TIA-1) in order to

identify and quantify cells that are infiltrating into renal allografts and playing a role in acute renal allograft rejection. Additionally, the role of GMP-17 in graft vs. host disease is also well-known in the art (see, for example, Lipman *et al.*, J. Immunol. 1994, 152:5120-5127, a copy of which is attached for the convenience of the examiner). As is illustrated in the subject application, the 53 N-terminal amino acids of SEQ ID NO: 42 are identical to the first 53 amino acids of GMP-17 (see paragraph 703). Thus, it is respectfully submitted that one skilled in the art would recognize that antibodies to the N-terminal portion of SEQ ID NO: ID NO: 42 would specifically bind not only SEQ ID NO: 42, but also GMP-17. Thus, the polypeptide of the subject invention can be used to generate antibodies that are useful for the identification of cells infiltrating into renal allografts or cells involved in GVHD. Indeed, such uses are specifically indicated at paragraphs 712 and 713 (indicating that antibodies can be used to monitor the beginning of graft rejection or GVHD in a patient).

Claims 2 and 14-18 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Office Action states that the claimed invention is not enabled by the subject application and supports its position with the analysis that the claimed invention is not enabled because of "the large quantity of experimentation necessary to determine activity or property of the disclosed nucleic acid such that it can be determined how to use the claimed sequence, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, and the breadth of the claims which fail to recite a particular biological activities, the specification fails to teach the skilled artisan how to make and use the claimed invention. Applicants respectfully traverse and note that the rejection appears to be directed to polynucleotides rather than the claimed polypeptides.

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is

necessary, but whether, if experimentation is necessary, is it undue. *In re Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976).

As indicated *supra*, the subject application teaches the claimed polypeptide of the subject invention and a variety of uses for the subject invention, including the production of antibodies that find use in identification of activated cells associated with graft rejection and GVHD. In view of these teachings in the subject application and the state of the relevant art, it is respectfully submitted that one skilled in the art would know how to make and use the claimed invention given the high level of skill in this art. Furthermore, the breadth of the claims, directed to polypeptides comprising, or consisting of, amino acids 1 to 105 or 37 to 105 of SEQ ID NO. 42, and the predictability of being able to generate antibodies to a given polypeptide sequence do not support a finding that the subject application is not enabled with respect to how one is to make and use the claimed invention. Finally, it is respectfully submitted that the amount of experimentation necessary to identify antibodies that specifically bind to the polypeptides of the claimed invention and that are suitable for use in identifying activated cells involved in graft rejection and/or GVHD is not undue or burdensome. Accordingly, it is respectfully submitted that the subject specification does enable one skilled in the art to both make and use the claimed invention. Reconsideration and withdrawal of the rejection is respectfully requested.

The Office Action has also rejected claims 1 and 14-18 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonable convey to one skilled in the art that the inventor(s) were in possession of the claimed invention at the time the application was filed. The Office Action supports this conclusion on the grounds that:

> Claim 2 is directed to encompass fragments, a signal peptide sequence, and a mature polypeptide sequence of SEQ ID NO: 42 which do not meet the written description provision of 35 USC § 112, first paragraph. Due to open claim language "comprising" and "comprises" in claims 14, 15, and 18; the claims are directed to encompass polynucleotide sequences that do not meet the written description provision of 35 USC § 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

Applicants respectfully submit that the claims are not directed to polynucleotides and that the specification and claims met the written description requirements of 35 U.S.C. § 112, first paragraph for the following reasons. It is recognized that the terms "comprises" and "comprising" are open claim language; however, certain embodiments of the subject application and claims include the addition of components to the claimed polypeptides that provide for their multimerization (see, for example, paragraphs 141-144). Additionally, the claimed polypeptides can be fused to other heterologous polypeptides for the generation of antibodies (see for example, paragraph 172). Accordingly, it is respectfully submitted that the claimed invention, directed to a polypeptide comprising SEQ ID NO: 42 adequately supported by the written description of the subject application. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 2 was rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. Applicants respectfully submit that this rejection is moot in view of the cancellation of the claim.

Claims 2, 14, and 15 have been rejected under 35 U.S.C.§ 102(b) as being anticipated by Turman *et al.* Applicants respectfully traverse and note that this rejection is moot with respect to claim 2.

As relates to claims 14-15, it is well-settled case law that a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). In the case of the rejection of record, it is respectfully submitted that the cited reference fails to anticipate the claimed invention because it fails to teach each and every amino acid recited in the claimed invention. For example, the reference fails to teach an amino acid sequence comprising amino acids –37 to 105 or amino acids 1 to 105 of SEQ ID NO: 42 (see sequence alignment provided with Office Action of April 14, 2003 illustrating a gap between the claimed sequence and that of the prior art).

It is also noted that the Office Action indicates that the use of the transitional phrases "comprising" and "comprises" in the claims allows for the application of Turman *et al.* as prior art to the claimed invention because the reference teaches a fragment that is identical to a fragment of SEQ ID NO: 42. Applicants note that claims 14-15 do not contain a recitation of "fragment" and

respectfully submit that the reference fails to anticipate the claimed invention because each and every amino acid recited in the claims is not taught by the reference. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

In view of the foregoing remarks and the amendments to the claims, the applicants believe that the pending claims are now in condition for allowance, and such action is respectfully requested. The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Applicants also invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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Attachment: New pages 1-87 (Sequence Listing)